TOBACCO INDUSTRY RESEARCH COMMITTEE
150 EAST FORTY SECOND STREET NEW YORK 17, N. Y.

#219

Application For Research Grant

Date:

November 20, 1958

1. Name of Investigator:

Robert H. Linnell, Ph.D.

2. Title:

Associate Professor of Chemistry

3. Institution & Address:

University of Vermont
Burlington, Vermont

4. Project or Subject:

The Oxidation of Nicotine by Gaseous Oxygen: Mechanism, Products and Kinetics

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

Previous work by the applicant (unpublished) indicates that cotinine (N-methyl-2-(3-pyridyl)-5-pyrrolidone) is a major product of the O_2 oxidation of nicotine at temperatures near ambient (see Frankenburg, J.A.C.S. 72 149 (1957)). The reaction may proceed through a nicotine-oxygen complex (pi-electron complex) as is probably the case with pyrrole (see Linnell, Arch. Biochem. and Biophys. 57 264 (1955)). Low temperature nmr ultraviolet studies will be used to study the nicotine-oxygen complex. Infrared provides a convenient means for analysis of cotinine in the presence of excess nicotine (see Frankenburg above and Eddy and Eisner, Anal. Chem. 26 1428 (1954)) as well as detection and analysis of other nicotine derivatives. A vacuum system will be built to study oxygen uptake and determine if all the oxygen forms cotinine. The Kinetics of the reaction with oxygen will be followed by at a series of temperatures, near ambient temperatures. Pure cotinine will be prepared and used as a standard for infrared analysis; stability of cotinine to oxygen will also be investigated. Later studies are contemplated at higher temperatures where it is to be expected that complexities of mechanism and products will be found.

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6. Budget Plan:

Salaries	5,500.00
Expendable Supplies	1,500.00
Permanent Equipment	5,200.00
Overhead (18%)	2,220.00
Other (travel-publication)	400.00
Total	14,820.00

7. Anticipated Duration of Work: 18 months

8. Facilities and Staff Available: A Perkins-Elmer model 112 infrared instrument with both LiF and NaCl optics and associated equipment is available. Glass blowing and conventional laboratory facilities are quite adequate for this study. The chemistry department has a strong M.S. program (A.C.S. approved) and a research fellowship for 15 months (two semesters and two summers) is contemplated as part of the salary requirement; the project director accounts for the balance of salary requirements, to be free of summer teaching and work full time on this project during the summer of 1959. The project is currently under way as a senior thesis.

9. Additional Requirements:

Expendable supplies cover requirements for pyrex glass (stopcocks, standard taper joints, etc.), chemicals, dry ice and liquid air, thermostat equipment, infrared supplies, safety supplies, etc. Under permanent equipment a vacuum pump, special fume hood (because of highly toxic nature of nicotine) and ultraviolet spectral equipment is needed.

10. Additional Information (Including relation of work to other projects and other sources of supply):

The project director has his B.S. and M.S. (chemistry) from the Univ. of N.H. and his Ph.D. under Dr. W.A. Noyes at the Univ. of Rochester, and has worked with the physical-organic chemistry of N-heterocyclics (Photochemistry: Pyridine-Acetone, J.A.C.S. 73 3986 (1951); Pyridine-Pyrrole H-Bonding, J. Chem. Phys. 21 179 (1953) and ibid. 23 93 (1955); Anabasine, J.A.C.S. 76 1391 (1954); Polarographic Studies on Bipyridines, J.A.C.S. 77 6207 (1955); Tetramethyl bipyridine, J. Org. Chem. 22 1691 (1957); other publication in process on The Reaction of Sodium with Pyridine, Pyrolysis of Pyridine, 2,3-Biquinoline, U.V. of N=C-C=N compounds in H_2SO_4.) Currently H-Bonding studies are underway with Pyrrole and various pyridines, using infrared and a series of temperatures so as to evaluate ΔF, ΔH and ΔS. This work is supported by Research Corporation.

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Signature /s/ Robert H. Linnell
Director of Project

/s/ Howard M. Smith, Jr.
Secy. Division of Research in the Physical Sciences

/s/ L. R. Zinley
Business Officer of the Institution

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Recent statistical studies have linked certain types of tobacco use with health problems, in a cause and effect relationship. These studies suggest a difference in cigarette, cigar and pipe tobacco use. A great deal of work must be done to clarify and explain these statistics. It is interesting to note, however, that cigar tobacco is treated by a fermentation process during which time nicotine greatly decreases and some cotinine is formed. The physiological actions of cotinine have not been studied. There may be a relationship here to the health problem.

Obtaining information on nicotine oxidation products and kinetics would be a step in the direction of further understanding of these complex problems.

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